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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,281	01/20/2006	Fabienne Guehenneux	1017753000214	9227

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BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
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EXAMINER	
SNYDER, STUART	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,281	GUEHENNEUX ET AL.	
	Examiner	Art Unit	
	Stuart W. Snyder	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-54* is/are rejected.

7)☒ Claim(s) *19,20,38,40,41,45,46,50 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/13/2006 & 1/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 19-54 as amended on 1/20/2006 are subject to examination

Claim Objections

2. Claims 38, 40-41, 45-46, and 50-51 are objected to because of the following informalities: The claims recite "live or attenuated vaccine"; this is a *non-sequitur* because attenuated viruses can be live or inactivated and live viruses can be fully virulent or attenuated—there is no choice between live and attenuated vaccines. Appropriate correction is required.

3. Claims 19-20 are objected to because of the following informalities: The claims recite "recombinants derivatives", an apparent typographical error. Appropriate correction is required.

4. Claims 24-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are drawn to a method of producing a vaccine in avian embryonic stem cell lines and limit the method by stipulating the method of producing the stem cells. It is unclear how the method of producing the stem cells limits the base claims because it is entirely within the realm of possibility to produce the cells by other means (see for example the method of producing stem cells in the 102(b) rejection below. Applicants' attention is drawn to claims 30-36 wherein the

characteristics of the cells have a direct impact on the method of producing the vaccine and the quality of the resultant vaccine. Thus, the metes and bounds of the claim cannot be determined with the current claim language. Correction is required.

5. Claim 34 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim depends on Claim 19 recites "avian cell lines are cultivated in basal medium" whereas Claim 19 recites, in reference to the avian cell lines, "culturing...in a basal medium". Although the words used in each claim are slightly different, there is no further limitation of Claim 19 by Claim 34.

Claim Rejections - 35 USC § 112, 1st ¶

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 44, 49 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention: The invention is drawn to a method of producing an anti-cancer vaccine using an Orthopoxvirus propagated in non-adherent avian embryonic stem cells.

State of the prior art: At the time of the claimed invention, methods were known for producing avian embryonic stem cells, propagating Orthopoxviruses in avian embryonic cells and producing a discreet number of Orthopoxvirus-based anti-cancer vaccines (see citations in 103 rejection below).

Breadth of the claims: The claims are broadly drawn to a genus of Orthopoxvirus-based vaccines, anti-cancer, produced in the aforementioned cells.

Working examples: No working examples are given.

Guidance in the specification: Specific guidance is given for production of avian embryonic stem cells; no guidance is given for manipulation of Orthopoxvirus genome other than reference to external sources or the types of cancer antigens to be inserted into the genome necessary for production of an anti-cancer vaccine. No steps are included in the claimed method.

Predictability of the art: No effective anti-cancer vaccine is licensed for treatment of cancer; a limited number of antiviral vaccines are available for prevention of cancer most notably anti-HPV vaccines (see, for example, Chabocovsky and Ryle, complete reference especially Introduction).

Amount of experimentation: Substantial experimentation may be necessary to produce an effective anti-cancer vaccine using the Orthopoxvirus platform other than those based on existing vaccines.

Given the breadth of the claims, the lack of guidance in the specification, and the predictability of the art, it would require undue experimentation for one skilled in the art to use the claimed composition and method.

Claim Rejections - 35 USC § 112, 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 recites, "wherein said recombinants derivatives are native or recombinant vaccinia virus". It is unclear how a recombinant derivative poxvirus can be a native vaccinia virus. The term "recombinant" clearly indicates that the virus is not a native virus (i.e., a virus found in nature that is not modified). The metes and bounds of the claim cannot be determined with the current claim language. Correction is required.

8. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: No additional steps are included in the claim relative to Claim 19; thus the critical step required for use of the method to produce a smallpox vaccine is lacking.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 19, 21, 23, 30-35, 37-40, 43-45, and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Barban and Aujame. The claims are drawn to a method of producing a vaccine, especially an anti-smallpox vaccine, in avian embryonic stem cell lines. Dependent claims further limit the claimed invention by including steps of inoculating avian embryonic stem cell lines with an MOI between 0.01 and 0.5, culturing the cells in basal medium until cell lysis occurs, specifying that the cells are able to proliferate in medium variously free of exogenous growth factors, serum (or both), basal medium (specified as one of DMEM, GMEM, HamF12 or McCoy).

Barban and Aujame teaches production of ALVAC, an anti-smallpox vaccine, in avian embryonic stem cell. Barban and Aujame further teaches steps of inoculating avian embryonic stem cell lines with an MOI of 0.1 (see page 4, paragraph 71, Barban and Aujame), culturing the cells in basal medium until cell lysis occurs (see page 4, paragraph 71, Barban and Aujame), and specifying that the cells are able to proliferate in DMEM/F12 medium free of exogenous growth

factors (see page 5, paragraph 61 referencing DMEM/F12 an exogenous growth factor free medium, Barban and Aujame), serum (or both (see page 5, paragraph 78, Barban and Aujame).

Claim 44 is drawn to a method of producing a live or attenuated (see objection regarding live or attenuated) Orthopoxvirus vaccine in non-adherent avian stem cells. Claim 44 depends from claim 40, which refers to the use of non-adherent cell lines established in step c) according to the method of claim 30. The Office does not consider the method of establishing the non-adherent, avian stem cells (product by process) to be limiting. With regard to the intended use recited in claim 44, "for producing a vaccine against cancer", the limitation is not an active step and is therefore not considered to be limiting.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 19-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lovas and Hollos and Mayr, *et al.* in view of Pain, *et al.*, Barban and Aujame, and Ferber. The claims are drawn to a method of producing vaccinia virus, especially MVA, for smallpox vaccine production in avian embryonic stem cells. The method comprises, considering all of the limitations the steps of inoculating the cells with virus at an MOI between 0.01 and 0.5, culturing the cells in a basal medium until

cell lysis released viral particles into the medium. Additional limitations include native or recombinant vaccinia virus (specifically MVA); a particular method of producing the cells (see claims 24-29) that are inconsequential to the method (see section 4 above, 112 rejection); characteristics of the cells (able to proliferate in exogenous growth factor free/serum free medium (including DMEM, GMEM, HamF12 or McCoy), having one of the following characteristics: high nucleo/cytoplasmic ratio, endogenous alkaline phosphatase or telomerase activity, or reactivity to SSEA-1, SSEA-3 or EMA-1 antibodies; and producing a vaccine against cancer.

It has long been known that vaccinia replicates in chicken embryos for the purpose of basic studies and for smallpox vaccine preparation; Lovas and Hollos teaches replication of vaccinia virus in the embryonic egg. "Wild-type" vaccinia virus replicates in various mammalian and other cell lines, such as MDKC (see, Mayr, *et al.* and references therein) however the virus is virulent in most mammalian cells and it has long been thought that some mammalian cell lines carry other mammalian viruses capable of transformation, such as SV40 (see Ferber. Thus, other, non-mammalian cells lines have been used for virus replication such as the CEF cell lines used by Mayr, *et al.* in development of MVA as an attenuated viral smallpox vaccine. Neither Lovas and Hollos nor Mayr, *et al.* teach replication of vaccinia in chicken embryonic stem cell lines. Pain, *et al.* teaches development of an avian (Gallus sp.) embryonic stem cell lines (CES). The method involved obtaining chicken blastodermal cells, applying them onto

inactivated STO feeder cells, removing the cells and replating them onto gelatin coated dishes, removing non-adherent cells, culturing with growth factors, then in some cases removing growth factors. Pain, et al. further teaches that the derived cells inherently posses the ability to express alkaline phosphatase (see page 2341, second paragraph under Results), telomerase activity (see page 2344, Figure 5 and following paragraph) and epitopes that bind SSEA-1 (see page 2343, Figures 3 and 4). The teachings of Barban and Aujame are outlined above and include the limitations of cell proliferation on specific media.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Lovas and Hollos and Mayr, *et al.* for producing smallpox vaccine by using CES for replication of the virus as taught by Barban and Aujame and Pain, *et al.* The skilled artisan would have been motivated to do so to avoid potential pathogenic virus propagation of other cell-lines used, as taught by Ferber (whole article). There would have been a reasonable expectation of success, given replication of vaccinia in chicken embryonic blastodermal cells, as taught by Lovas and Hollos. Thus, the invention of as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is

advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart W. Snyder whose telephone number is (571) 272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stuart W Snyder
Examiner
Art Unit 1648

sws

/Stacy B. Chen/ 7/9/2007
Primary Examiner, TC1600